Precision Olfactory Delivery (POD®) of Drugs for Neurological Disease: A Safety, Tolerability and Comparative Bioavailability Study of POD Dihydroergotamine Mesylate (INP104) to Approved IV D.H.E. 45® and Migranal® Nasal Spray.

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Objective: Impel NeuroPharma has developed the Precision Olfactory Delivery (POD®) device to achieve consistent medicine delivery to the upper nasal cavity giving rapid uptake and higher bioavailability relative to standard nasal sprays. This study with dihydroergotamine mesylate (DHE) for migraine treatment compares safety, tolerability, bioavailability and pharmacokinetics (PK) of INP104 with IV and traditional nasal delivery of DHE.

Background:
INP104, a drug-device combination product, delivers an approved DHE formulation to the upper nasal cavity by POD device. DHE is a proven treatment for migraine, effective in many therapy-resistant situations, but hampered by inconvenient and undesirable delivery by injection or inconsistent bioavailability (BA) from delivery to the lower nasal cavity (Migranal claims 32%).
Design/Methods: A 3-way, 3-period, 6-sequence study was conducted in healthy volunteers with safety, assessments and PK collections for 48 hours post dosing and 7-day wash outs.

Results: 38 enrolled, 27 datasets obtained. DHE plasma levels following 1.45 mg INP104 administration rapidly increased to match mean plasma DHE levels of 1.0 mg D.H.E. 45 IV by 30'. At INP104 T_{max}, mean C_{max} was 1301 pg/mL ($C_{30'}$ 1224 pg/mL with IV). Migranal 2.0 mg C_{max} was 299.6 pg/mL at 47 min. $AUC_{0\text{-}inf}$ were 6275, 7490 and 2199 h*pg/mL with INP104, IV and Migranal, respectively. The ratio of the geometric means were 0.08 and 0.74 (INP104: IV for C_{max} and $AUC_{0\text{-}inf}$) and 4.45 and 3.08 (INP104: Migranal and BA ($AUC_{0\text{-}inf}$) 58.9%; Migranal 15.2%. TEAEs, mostly mild, were reported by 15 (48.4%), 21 (65.6%) and 14 (41.2%) subjects after INP104, IV and Migranal with 6, 16 and 4 considered possibly/probably related. INP104 was preferred by 69%.

Conclusions:
Satisfactory safety, tolerability, bioavailability and patient preference led to the IND filing for INP104 in 2018 and initiation of a final phase 3 safety study requested by the FDA for an NDA.